An alternative electroretinography protocol for children: a study of diagnostic agreement and accuracy relative to ISCEV standard electroretinograms

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ABSTRACT.

Purpose: To assess the diagnostic accuracy and agreement between a paediatric electroretinography protocol used at Great Ormond Street Hospital (GOSH-ERG) and the ‘gold standard’ international protocol (ISCEV-ERG) in health and disease.

Methods: Patient databases between 2010 and 2020 were screened to identify children with an ISCEV-ERG recorded within four years of a GOSH-ERG. Electroretinogram (ERG) component peak times and amplitudes were re-measured, and data were analysed in terms of absolute abnormality and proportional deviation from respective reference ranges. Abnormality was defined by the retinal system affected and by individual ERG a- and b-wave component analysis.

Results: A total of 59 patients were included: 38 patients had retinal disease defined by an abnormal ISCEV-ERG and 21 had normal ISCEV-ERGs. When absolute abnormality was defined by combined retinal systems, the GOSH-ERG showed an excellent overall sensitivity of 95% (accuracy 86%). Individual retinal systems showed good–excellent sensitivity (67%–100%) and specificity (68%–97%). Electroretinogram (ERG) component sensitivities ranged between 60% and 97% and specificities between 79% and 97% dependent upon the protocol step. The proportional relationship appeared mostly linear between protocols. Electroretinogram (ERG) morphology was comparable for both protocols in a range of retinal diseases including those with pathognomonic ERGs.

Conclusion: We demonstrate the high diagnostic accuracy of a paediatric ERG protocol (GOSH-ERG) relative to ISCEV standard ERGs. The close proportional deviation and similar waveform morphology indicate ERGs from each protocol are similarly affected in disease. This encourages the use of the GOSH-ERG protocol in the screening, diagnosis and monitoring of retinal disease in children who are unable to comply with the rigorous ISCEV-ERG protocol.

Key words: electroretinography – paediatric – retinal disease – retinopathy – GOSH-ERG – ISCEV-ERG

Introduction

The full-field flash electroretinogram (ERG) is a widely used diagnostic test of generalized retinal function. The flash ERG can identify a functional abnormality within the retina. It is typically recorded to protocols described by the International Society for Clinical Electrophysiology of Vision (ISCEV) ERG standard (McCulloch et al., 2015), which facilitates international communication and comparison. This standard specifies the stimulus and recording parameters for six recording protocols, which bias or preferentially elicit responses from different retinal systems to identify the locus and extent of retinal dysfunction. The ISCEV-ERG standard is regularly updated and is an important step to standardize work across international laboratories (Hamilton, et al., 2015).

Whilst the ISCEV-ERG standard can be applied successfully in young children, by swaddling babies or dark adapting in a different room whilst taking consent under red light, it is a lengthy test (Fulton, Hartmann & Hansen, 1989; Tremblay & Parkinson, 2003; Bradshaw, Hansen & Fulton, 2004; van Genderen et al., 2006). The ISCEV-ERG standard acknowledges it is not easy to apply in ‘non-compliant children between 2 and 5yrs’ and abbreviated protocols may be necessary (Fulton, Hartmann & Hansen,
1989; Parness-Yossifon & Mets, 2008). Some centres suggest the tests are delayed until children are old enough to comply and refer to the ‘toddler dip’ when ERGs are not performed (van Genderen et al., 2006). The ISCEV-ERG standard protocol requires a period of dark adaptation (DA) and light adaptation (LA) lasting 20 and 10 min, respectively, alongside pupil dilation, a fixed position looking into a Ganzfeld bowl for flash stimulation, and ideally corneal electrodes. Skin electrodes are now included as a less invasive option in the most recent standard update (McCulloch, et al., 2015). The ISCEV-ERG standard is preferred, but due to the long test time some authors have explored shortening the DA period to 10 min. This has been shown to have little effect on the mixed rod cone DA3 ERG and reduces the amplitude of the rod-driven DA0.01 ERG b-wave by 10%–13% (Hamilton & Graham, 2016; Bach, Meroni & Heinrich, 2020). Likewise, the LA period has been reduced to 5 min with little effect on the LA3 response (Asakawa et al., 2019), though differences in peripheral and central retina LA timing have been reported (Kondo et al. 1999). To date, these alterations to the ISCEV-ERG protocol have been in healthy participants only and have not been verified in patients with retinal disease. Alternatively, some centres therefore choose to perform paediatric ERGs under anaesthesia, circumstances that can influence the ERG b-wave (Andreasen et al., 1993; Tremblay & Parkin-son, 2003; Ioham et al. 2004; Messenger, Yang, & Pennesi, 2014) alongside having potential immediate (cardiorespiratory) and uncertain long-term effects on neurocognitive development (O’Leary & Warner, 2017). Others seek to introduce individual elements of the ISCEV-ERG standard gradually as compliance allows (Holder & Robson, et. al., 2006). Others, such as our centre, who do not have sedation or anaesthesia resources available, choose to use abbreviated and modified paediatric ERG protocols until an alert child is able to comply with the standard ISCEV-ERG test in full.

Tony Kriss first published a modified paediatric ERG protocol (GOSH-ERG) in 1992, and it has been adopted in a number of centres, including Great Ormond Street Hospital for Children for the investigation of paediatric retinal disease (Kriss & Russell-Eggitt, 1992; Kriss et al., 1992; Kriss, 1994). We have updated the protocol in line with changes in the ISCEV-ERG standard, including the addition of a stronger flash. The GOSH-ERG protocol has been developed to produce similar responses to an ISCEV-ERG in a 10 min test time. In brief, it adapts the test delivery so that it is acceptable to an alert child without sedation or anaesthesia by using skin electrodes with minimal dark adaption (<5 min), and natural pupils to allow pattern visual evoked potential (pVEP) testing in the same appointment. The proportional contributions of specific rod and cone retinal systems are biased by modifying background lighting, stimulus flash strength and chromaticity. The use of red and blue flashes has been used widely in paediatric practice by other units (Fulton, Hartman, & Hansen, 1989; Breeijl & Stirn-Kranjc, 2004). The flash stimulus is produced by a handheld stroboscope or LED stimulator, which can be moved easily to follow the head movements of a child with natural pupils, although the examiner should be aware of the inhomogeneity of the flash luminance source and variable gaze direction, which may influence retinal illumination and theoretically affect diagnostic sensitivity.

Whilst the GOSH-ERG protocol has been used over many years providing comparable diagnostic results in clinical practice, its diagnostic accuracy has not been validated against the ‘gold standard’ of the ISCEV-ERG. This validation is timely and necessary in this genomic era, when treatments of retinal disease and systemic disease associated with retinal dysfunction are translating rapidly into practice. Early diagnosis is ever important. Increasingly, ophthalmologists are being asked to catalogue the retinal phenotype and natural history of children in the non-compliant age range (18 months-5 years) in preparation for treatment trials. The growing independence of children in this age range alone makes them less compliant and tolerant of an ISCEV-ERG protocol, but if they also have systemic disease associated with neurodevelopmental delay or autistic spectrum behaviours, their ability to comply with the exactitude of position and duration of an ISCEV-ERG is severely reduced and a meaningful alternative ERG method is needed.

Our study aimed to evaluate the diagnostic agreement between GOSH-ERG and ISCEV-ERG protocols and to inform clinicians about the diagnostic accuracy of this modified paediatric ERG protocol.

**Methods**

A retrospective case note review was conducted for all patients who had a GOSH-ERG over a ten-year period (2010–2020). These data were screened to identify those patients who had a ‘gold standard’ ISCEV-ERG within four years of the GOSH-ERG recording date. The GOSH-ERG and ISCEV-ERG waveforms were re-measured by an experienced scientist for peak time and amplitude of the a-wave and b-wave components for each eye. Data were considered abnormal if they fell outside of the laboratory reference ranges for each respective ERG protocol. The analysis comprised of two main considerations, one for absolute abnormality (i.e. normal or abnormal response) and also in relative terms (i.e. proportional deviation away from reference limit, such as amplitude lower limit or peak time upper limit). Electroretinograms (ERGs) from each eye were considered together, with an abnormal ERG result considered when responses fell outside the reference limits for both eyes. For measuring proportional deviation from the reference value, each eye of each patient was considered separately.

The GOSH-ERGs were recorded according to our previously published protocol (Kriss & Russell-Eggitt, 1992). In brief, the patient has a visual evoked potential recording in a darkened room prior to ERG testing, and this begins dark adaptation. Skin electrodes are applied just below the lower lids, typically referred to an outer canthus electrode. A handheld flash stimulator (PS33 Photic Stimulator, Grass Instruments) presents flashes at 3Hz, initially with a moderate intensity (GR4 setting; ~5 cd.s.m⁻²) 30cm away from the eyes to produce a mixed rod-cone response under scotopic conditions (room lit by the TV only). The room lighting is then darkened further, by turning off the TV, and a dim blue flash (GR1 setting; ~0.1 cd.s.m⁻²; Wratten filter 47 ~440 nm) is presented at 30cm to
Table 1. Equivalent flash protocols between GOSH-ERG and ISCEV-ERG protocols for each major step of recording.

<table>
<thead>
<tr>
<th>GOSH-ERG protocol</th>
<th>ISCEV-ERG protocol</th>
<th>Collective term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scotopic predominantly rod-driven (dim blue flash GR1)</td>
<td>DA 0.01</td>
<td>Rod-driven response</td>
</tr>
<tr>
<td>Scotopic mixed (moderate white flash GR4)</td>
<td>DA 3</td>
<td>Scotopic mixed rod cone</td>
</tr>
<tr>
<td>Scotopic maximal flash (bright white flash GR16)</td>
<td>DA 10</td>
<td>Scotopic bright flash</td>
</tr>
<tr>
<td>Photopic cone (moderate white flash GR4)</td>
<td>LA 3</td>
<td>Photopic cone</td>
</tr>
<tr>
<td>Photopic 30 Hz (moderate white 30 Hz GR4)</td>
<td>LA 30 Hz</td>
<td>Photopic 30 Hz ficker</td>
</tr>
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Table 2. Definitions of abnormality defined by system (top tier) and individual component (bottom tier) in analysis.

<table>
<thead>
<tr>
<th>Abnormality by system</th>
<th>GOSH-abnormality</th>
<th>ISCEV-ERG abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rod system</td>
<td>GOSH-abnormality</td>
<td>ISCEV-ERG abnormality</td>
</tr>
<tr>
<td>Rod photoreceptors</td>
<td></td>
<td></td>
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<tr>
<td>Cone system</td>
<td></td>
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<tr>
<td>Inner-retina</td>
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<tr>
<td>Rod-driven b-wave</td>
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<tr>
<td>Scotopic rod-driven b-wave</td>
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<td>Scotopic maximal flash a-wave</td>
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<tr>
<td>Photopic cone a- and b-waves</td>
<td></td>
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<tr>
<td>Photopic 30 Hz waveform</td>
<td></td>
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<tr>
<td>Rod-driven b-wave</td>
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<tr>
<td>Scotopic rod-driven b-wave</td>
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<td>Scotopic maximal flash a-wave</td>
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<td>Photopic cone a- and b-waves</td>
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<td>Photopic 30 Hz waveform</td>
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</table>

Results

A total of 59 patients had both GOSH and ISCEV-ERGs recorded within 4 years. Of this cohort, 38 patients had abnormal ISCEV-ERGs (cone dysfunction/dystrophy n = 10, cone-rod dystrophy n = 2, rod-cone dystrophy n = 7, incomplete congenital stationary night blindness (ICSNB) n = 12, complete CSNB (cCSNB) n = 5, enhanced S-cone syndrome n = 1 and KCVN2 retinopathy n = 1) and the remaining 21 patients had normal ISCEV-ERGs. The median time in days between GOSH-ERG and ISCEV-ERG was 47 days (range: −581 to 1378 days, IQR: 0−254 days). The median age of this patient cohort was 9.9 years (range: 5.1−22.8, IQR: 8.1−12.9) and ISCEV-ERG was 10.3 years (range: 6.0−22.8, IQR: 9.9−13.4). Based upon our clinic patient audits, the majority of patients seen with GOSH-
ERGs are <5 y/o, mostly 1–3 y/o, though some patients continue to be seen at our tertiary referral centre into young adulthood due to rare and often complex medical conditions.

Analysis of absolute abnormalities

Figure 1 shows the receiver operating characteristic (ROC) curves for analysis by system and by individual component; qualitative terminology for accuracy findings, such as excellent or good, is consistent with those defined by the International Federation of Clinical Chemistry and Laboratory Medicine (Simundić, 2009). The ROC curve is a performance measurement of a diagnostic test. It plots sensitivity (the true-positive rate) on the y-axis against 1-specificity (false-positive rate) on the x-axis. The closer the plot is to the top left corner, the better the test performance. The point of the plot nearest the top left corner is the best compromise between sensitivity and specificity, in other words the most accurate point for diagnosing an outcome – the Youden index. If the plot falls on the diagonal axis, where y = x (i.e. bottom left to top right), this indicates a poor performance as the test produces false-positive result at the same rate as true-positive result (Altman & Bland, 1994; Schisterman et. al., 2005). The area under the plotted curve (AUC) is a global measure of a test ability to discriminate if a condition is present or not, in this circumstance the ability to discriminate retinal dysfunction. An AUC of 0.5 means discrimination is not better than chance, whilst AUC of 1 is perfect discrimination.

Overall, the ROC curves of ERG data demonstrated good–excellent classification of GOSH-ERG against the ISCEV-ERG. In terms of system abnormality, the GOSH-ERG protocol showed high accuracy in all measures, most notably in the detection of ‘rod system’ or ‘cone system’ abnormalities with sensitivities of 93% and 100%, respectively. In terms of component abnormalities, the rod-driven b-wave showed high accuracy at 0.95 and sensitivity at 93%, and other specific measures showed good or high accuracy ranging between 0.7 and 0.9. The sensitivity of these less accurate components was high, with the cone-mediated responses having 92% sensitivity for the photopic cone ERG and 97% sensitivity for photopic 30Hz flicker. The scotopic bright flash ERG had the lowest sensitivity at 61%, but high specificity at 88%, which is important when considering the high sensitivity of the rod-driven response as a complementary rod system ERG measure. The AUC measurements showed high global accuracy of the GOSH-ERG protocol relative to the ISCEV-ERG.

Table 3 data are presented with abnormality defined in absolute terms. The abnormality by system rows shows very high or excellent diagnostic accuracy ranging between 0.86 and 0.95, and slightly less but still high diagnostic accuracy for abnormality by component, ranging between 0.72 and 0.95. Abnormality by system AUC data shows all relationships have very good or excellent accuracy (ranging between 0.80 and 0.95). Abnormality by component demonstrates a wider range between good and excellent global accuracy (0.74–0.95), with all measures showing very good or excellent accuracy, with the exception of the scotopic bright flash response, which showed good accuracy. The discrepancy between the accuracy of rod photoreceptor and scotopic bright flash responses in system analysis and component analysis, respectively, suggests the scotopic bright flash response b-wave is less comparable to the DA 10 ISCEV-ERG b-wave, as the a-wave (i.e. that reflected in rod photoreceptor system) had very good accuracy. The ability of the scotopic mixed rod-cone ERG

Fig. 1. Receiver operating characteristic (ROC) curves for GOSH-ERG and ISCEV-ERG accuracy. The left figure illustrates the relative accuracy of the GOSH-ERG against ISCEV-ERG when defining abnormality by retinal systems. Each system is defined by its respective colour with an abnormality in ‘any system’, that is overall sensitivity, seen from the black line. The right figure illustrates the relative accuracy of the GOSH-ERG against ISCEV-ERG when defining abnormality by individual components.
to detect any retinal abnormality was also separately analysed, as this single ERG step may be suitable for screening or for patients who are particularly challenging to test. Analysis at the ocular level demonstrated the mixed rod-cone ERG to have excellent sensitivity and specificity (94.7% and 92.9%, respectively) in detecting any retinal abnormality (i.e. abnormal peak time, amplitude or b:a ratio), with excellent PPV and NPV also (96% and 90.7%, respectively). Those eyes producing an abnormal GOSH-ERG scotopic mixed rod-cone but normal ISCEV-ERG (3/42 eyes) had normal amplitudes, but peak times were 1ms early or later than the reference range. The mixed rod-cone ERG b-wave peak time was overall delayed in those patients with cone dysfunction (mean ± SEM; 43.4 ms ± 1.2 ms), and atypically early in those with rod-cone dysfunction (36.4 ms ± 2.1 ms), in keeping with the dependence of b-wave peak time on the proportional balance of rod versus cone contribution.

Analysis of relative abnormalities

The degree of abnormality or deviation was plotted for each major component (from a- and b-wave component analysis) and displayed in Fig. 2. The data in Fig. 2 demonstrate a consistent, mostly linear relationship of the proportionate deviation from the reference limits for corresponding GOSH-ERG and ISCEV-ERG protocol steps. The majority of peak time differences of the rod system b-waves fell within normal limits. Of the data points that fell outside the linear trend, most evident were the photopic cone b-wave amplitudes, which tended to demonstrate a higher degree of abnormality in the ISCEV-ERG than in the GOSH-ERG. Nevertheless, the photopic cone amplitude plot has narrow 95% confidence bands, which trend linearly and overall suggest good proportional agreement. These data demonstrate the high accuracy of the GOSH protocol in terms of ERG retinal systems, which form the clinical diagnosis, alongside the individual components measured. However, importantly in clinical practice, subtle alterations of ERG waveform morphology can also contribute to a diagnosis. Therefore, example ERG waveforms produced by patients from each of the main diagnostic categories found in this cohort are provided in Fig. 3. ISCEV-ERG and GOSH-ERG waveforms are overlaid for comparable protocol steps. This demonstrates the similarity of ERG waveform morphology in both techniques for childhood retinal dysfunction, including two patients with pathognomonic waveforms of enhanced S-cone syndrome and KCNV2 retinopathy. Responses were scaled appropriately, with GOSH-ERGs scaled to 10% of ISCEV-ERGs, similar to published values of around 12% (Esakowitz et al., 1993).

Discussion

This within-subjects study compared a modified protocol for recording paediatric electroretinograms (GOSH-ERG) against the gold standard (ISCEV-ERG) protocol and found the GOSH-ERG showed very good or excellent overall diagnostic agreement with ISCEV-ERG both in terms of abnormality of retinal systems and individual components. Furthermore, we have demonstrated there is a proportionate degree of abnormality from each protocol, with comparable waveform morphology from the GOSH-ERG to ISCEV-ERGs.

The GOSH-ERG protocol has been used successfully since its inception to evaluate retinal function in infants and children and to provide long-term monitoring and phenotyping of disease (Jacobs, et al., 1992; Kriss & Russell-Eggitt, 1992; Kriss, 1994; Lavy, et al., 1995; Thompson, et al., 2013). Although some studies have used both the GOSH-ERG and ISCEV-ERG protocols in children (Kurent et al., 2015), there has not been to date an empirical comparison with internationally accepted ISCEV-ERG standards, to demonstrate the relative diagnostic accuracy of these measures.

The GOSH-ERG protocol demonstrated excellent overall accuracy relative to ISCEV-ERGs in terms of abnormality by retinal system analysis. The ‘systems analysis’ approach is typically used in clinical practice. It considers corroborating information from each step in the protocol to identify an abnormality of retinal systems and classify a retinal dysfunction, rather than depending upon a single isolated abnormality. As such, GOSH-ERGs identify abnormality in any retinal system with excellent sensitivity and with excellent and perfect

### Table 3

<table>
<thead>
<tr>
<th>Abnormality by System</th>
<th>Accuracy of GOSH protocol</th>
<th>95% CI for accuracy</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rod system</td>
<td>0.95</td>
<td>(0.8562, 0.9892)</td>
<td>0.93</td>
<td>0.97</td>
<td>0.96</td>
<td>0.93</td>
<td>0.95</td>
</tr>
<tr>
<td>Rod photoreceptors</td>
<td>0.86</td>
<td>(0.7462, 0.9385)</td>
<td>0.67</td>
<td>0.93</td>
<td>0.77</td>
<td>0.80</td>
<td>0.80</td>
</tr>
<tr>
<td>Cone system</td>
<td>0.91</td>
<td>(0.8102, 0.9714)</td>
<td>1.00</td>
<td>0.79</td>
<td>0.87</td>
<td>1.00</td>
<td>0.90</td>
</tr>
<tr>
<td>Inner retina dysfunction</td>
<td>0.87</td>
<td>(0.7552, 0.9473)</td>
<td>0.74</td>
<td>0.94</td>
<td>0.88</td>
<td>0.87</td>
<td>0.84</td>
</tr>
<tr>
<td>Abnormality in any system</td>
<td>0.86</td>
<td>(0.7462, 0.9385)</td>
<td>0.95</td>
<td>0.68</td>
<td>0.86</td>
<td>0.87</td>
<td>0.82</td>
</tr>
</tbody>
</table>

The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) are reported for each protocol component. The AUC values reflect the area under the curve within the respective ROC curves produced. Diagnostic accuracy is provided in the far left column.
sensitivities in rod and cone systems (95%, 93% and 100%, respectively). This is particularly important for early diagnosis of retinal dysfunction, as the GOSH-ERG is a preferred first investigation in ‘non-compliant’ patients who are too young (i.e. within the ‘toddler dip’) or otherwise unable to tolerate the exactitude of a standard ISCEV-ERG recording, meaning a high sensitivity is required for the early detection of disease. In addition, we found excellent specificity of the rod photoreceptor systems from a-wave measurements of 93%, complementing the high rod system sensitivity. These findings were supported by the ROC curves, which demonstrated good–excellent area under curve (AUC) findings in all abnormality classifications, either by system or by component. We also found very good and excellent agreement, albeit less than in ‘systems’ analysis, for individual component analysis. In particular, the measurements of rod-driven responses and cone-mediated responses had excellent sensitivities of 93% and 92%, respectively. Whilst the scotopic bright flash had sufficient sensitivity (61%), it had very good specificity (88%), which complements the excellent sensitivity of the rod-driven response in characterizing the site of retinal dysfunction in these patients.

We did find low negative predictive values (NPVs) in the scotopic mixed rod-cone and scotopic bright flash component analysis, which is an interesting finding. However, as is performed in practice, data are not interpreted in isolation and ERGs must be interpreted as a constellation of features, as employed in our ‘systems’ analysis approach. As such, when these abnormalities are considered as a retinal system, such as reflecting rod system, rod photoreceptors or cone system, we found very good, excellent and perfect NPVs of 0.93, 0.80 and 1.0, respectively. The scotopic mixed rod-cone GOSH-ERG is produced from a less dark-adapted retina than an ISCEV-ERG DA3 response; therefore, the proportion of cones contributing to the GOSH-ERG mixed rod-cone response is higher. The waveform shape supports this as the b-wave peak time is earlier and the b-wave shape is more sharply defined, evident in Fig. 3. Therefore, we suspect the low NPV in the scotopic mixed rod-cone response reflects the different balance of rod-cone contributions, which for the GOSH-ERG is biased towards being more cone mediated due to reduced DA and higher stimulation rates (3Hz) relative to the ISCEV-ERG DA3 response. Furthermore, the flash stimulator not being a uniform entire field (i.e. Ganzfeld bowl) may contribute to this discrepancy, perhaps reflecting different spatial inhomogeneities of rod and cone photoreceptor contributions to the recorded responses, though averaging and the variation of flash direction relative to the child will dampen this somewhat. Nevertheless, rod system ERGs [from scotopic rod-driven and maximal flash responses] were highly comparable and able to delineate rod system dysfunction with minimal DA. In addition, the independent ability of the scotopic mixed rod-cone ERG in detecting any retinal abnormality showed an excellent sensitivity and specificity (94.7% and 92.9%, respectively), suggesting this response has clinical use as the first protocol step of choice. The mixed rod-cone ERG low false positives were due to subtle peak time deviations of 1ms, which clinically may be attributed to ocular pigmentation (Abdleseaed et al., 2010). Furthermore, it was reassuring to observe that in two cases with pathognomonic ERG features (KCVN2 retinopathy and enhanced S-cone syndrome), the distinctive

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Fig. 2. Plots comparing proportionate differences between ISCEV-ERG and GOSH-ERG data fitted in using non-parametric locally weighted regression (LOESS). The system components are labelled along the top of the figures. Data are plotted for their relative deviation from the respective reference limits used within the study, normalized by percentage for the ISCEV-ERG (y-axis) and GOSH-ERG (x-axis). Data were fitted with a locally weighted regression (LOESS) line (blue) with 95% confidence bands (grey shading). The top row illustrates the amplitude differences between each system component, and the bottom row illustrates the peak time differences between the two protocols. The black graph line is the zero–zero intercept; therefore, those data points falling to the bottom left quadrant are within normal limits for both tests, those within the upper left quadrant suggest larger deviation from the reference value in the ISCEV-ERG than GOSH-ERG, and conversely those in the bottom right quadrant suggest larger deviation from the reference value in the GOSH-ERG than ISCEV-ERG. The data points demonstrate some scatter, however, the LOESS line demonstrates good correlation between each protocol.
Waveform features were observed in both GOSH-ERG and ISCEV-ERGs, the GOSH-ERG potentially providing a means for earlier diagnosis (Vincent et al., 2013).

The GOSH-ERG protocol allows paediatric or abbreviated ERG testing in a test time reduced to less than 10 min. Whilst we present strong findings to advocate its use, our experience emphasizes several technical factors, which must be considered by those wishing to incorporate this protocol into practice. Firstly, the choice of electrode is important to optimize the signal-to-noise ratio; pregelled electrodes can be more easily applied and have lower impedance than cup-based electrodes (Man, et al., 2020). Secondly, the potential confounding effect of eye position is particularly relevant for infants. As the ERG signal is maximal over the corneal apex through the pupil aperture, upward...
deviation of the eyes can reduce the ERG amplitude recorded from a lower lid electrode. It is therefore important to note eye position, if possible encourage downward gaze towards the flash stimulus, or interpret data incorporating any aberrant eye movements (Kriss, 1994). Furthermore, one must consider variance with ocular pigmentation and retinal illumination from no pupil dilation. Those with small pupils, darkly pigmented irides and/or fundi may have lower b-wave amplitudes, whilst those with large pupils, lightly or hypopigmented fundi may have a larger amplitude, or sometimes smaller amplitude photopic ERGs associated with the photopic hill phenomenon (Hamilton et al., 2007). Therefore, any photopic b-wave abnormalities should be investigated further by presenting photopic flashes of higher or lower stimulus strength to study the dynamic changes in the b-wave.

The median age of our cohort was around ten years. At this age, we expect a neurodevelopmentally typical child to reasonably tolerate the demands of an ISCEV-ERG, though some of our ISCEV-ERG cohort were as young as five years. The youngest patient to have successfully completed an ISCEV-ERG within our laboratory was 3 years old, although within this study the youngest patient included was around five to 6 years old. In our practice, more than 50% of patients presenting for visual electrophysiology tests are under 5 years, indeed the majority around 1–2 years of age falling within the ‘toddler dip’. In common with other centres specializing in paediatric medicine, many children have not only ocular but also systemic, neurological or metabolic conditions, which means test compliance is an important consideration. For this reason, we use the GOSH-ERG as a routine first test across the paediatric age range. It is less demanding than an ISCEV-ERG, and these data show it allows highly accurate and comparable diagnostic outcomes within a 10-min test period, without the need for anaesthetic, pupil dilation or corneal electrodes. It is encouraging, and perhaps implied from our findings, that shorter periods of DA or LA appear to only minimally change the observed ISCEV-ERG in healthy retina, reported in some studies that have also used skin electrodes and no mydriasis (Hamilton & Graham, 2016; Asakawa et al., 2019; Bach, Meroni & Heinrich, 2020). This is an exciting prospect for future ERG recording methods, though these findings await exploration in disease groups to ensure their validity. Early diagnosis and monitoring of retinal function are particularly relevant in this genomic era. The ERG may be used to identify likely therapeutic windows or as a functional outcome measure for gene therapy in inherited retinal and systemic disease. Our findings suggest that the overall sensitivity, specificity and close proportional relationship between the GOSH-ERG and ISCEV-ERG make the GOSH-ERG a practical outcome measurement in those patients who would otherwise not be able to tolerate ERG testing. Whilst we have not presented longitudinal data within this cohort, the proportional similarities between the ISCEV-ERG and GOSH-ERG infer that the GOSH-ERG is a valuable tool in the longitudinal monitoring of patients with retinal disease, and indeed, this is used clinically. It should be emphasized, however, that the GOSH-ERG and ISCEV-ERG are not directly comparable as the stimulus and recording properties differ.

The GOSH-ERG utilizes a now obsolete xenon flash stroboscope (PS33 Photic Stimulator, Grass Instruments) due to its ability to deliver bright flashes within a very brief time period. Whilst there were little further technological developments to compare to these original devices, a newer commercially available light-emitting diode (LED) flash stimulator is now available, which has been shown to provide comparable photometric and ERG responses using the GOSH-ERG protocol (Liassis et al., 2020). Lastly, corneal electrodes are a disadvantage for children. More pertinent within the current SARS-CoV-2 international pandemic, the need for infection prevention and control is crucial. It has been shown that SARS-CoV-2 is detectable within the tear film in 24% of patients with COVID-19 (Arora, et al., 2020). Therefore, disposable electrodes, such as the skin electrodes used for the GOSH-ERG protocol, minimize the risk of patient–patient cross-infection or laboratory contamination, alongside having much shorter application and test times, which minimizes close patient–clinician interactions. It has been shown more recently that the GOSH-ERG protocol can also be recorded using a handheld ERG system (RETeval, LKC Technologies, Gaithersburg, USA) with comparable findings to the conventional GOSH-ERG in paediatric practice, which may offer an alternative, useful point-of-care screening for retinal disease (Carter et al., 2020).

Conclusion
We present data that validate a modified paediatric ERG protocol, the GOSH-ERG, compared with the international standard ISCEV-ERG, in a clinical cohort of patients with and without retinal disease. These data advocate the GOSH-ERG protocol as a diagnostically accurate alternative for screening or when ISCEV-ERG testing is not practical in ‘non-compliant’ children. The benefits of the GOSH-ERG protocol include a reduced test time and lack of corneal electrodes, pupil dilation or formal DA. All of these advantages improve the test compliance and quality of ERG data recorded from less cooperative children.

References
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